American Journal of Hematology 53:11–17 (1996)

Postoperative Thrombotic Thrombocytopenic Purpura Following Cardiovascular Surgeries

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Among 47 patients with thrombotic thrombocytopenic purpura (TTP), 8 patients were diagnosed to have postoperative-TTP. Two patients underwent vascular surgery, 5 patients coronary artery bypass grafts, and 1 patient resection of myocardial sarcoma. Prior to surgery, all patients except one had normal hemograms and platelet counts, and blood smears showed no schistocytes. Five to 19 days after surgery, all 8 patients developed postoperative TTP, which clinical feature was characterized by unexplained progressive encephalopathy, thrombocytopenia, and microangiopathic hemolytic anemia. In addition, in 3 patients, progressive gangrene of the toes also developed. Four patients achieved complete remission following exchange plasmapheresis and 1 patient spontaneous remission. Due to complicated surgical settings after surgery, recognition of TTP was often delayed and it contributed to death in 3 patients despite treatment with exchange plasmapheresis. In view of occurrence of postoperative TTP following cardiac and vascular surgeries, pathogenic mechanism for postoperative TTP may be explained on the basis of injury of diseased endothelial surface and release of a humoral factor(s) that results in platelet aggregation in the capillaries and arterioles. Our experience with these cases indicates that TTP may occur as a serious complication of cardiac and vascular surgeries, and early recognition of the diagnosis and institution of exchange plasmapheresis are of paramount importance for favorable outcome. © 1996 Wiley-Liss, Inc.

Key words: thrombocytopenia, thrombotic thrombocytopenic purpura, cardiovascular diseases, postoperative thrombocytopenia

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening hematologic syndrome characterized by the pentad of microangiopathic hemolytic anemia (MAHA), thrombocytopenia, neurological abnormalities, fever, and renal failure. However, for all practical purposes, the first two clinical features should be sufficient diagnostic criteria since neurologic manifestation may be a late event and fever and renal failure are not always present. Besides, prompt initiation of treatment is urgent. Unless early diagnosis is established and exchange plasmapheresis, which is the most effective treatment [1–5], is instituted, the demise of the patient may occur in a short time.

Although TTP usually is of idiopathic origin without underlyng pathology, in some patients this disease has been associated with certain pathologic conditions, such as scleroderma, rheumatoid arthritis, systemic lupus erythematosus, polyarteritis nodosa, bacterial endocarditis, stomach cancer, and breast cancer [6–10]. TTP also has occurred with pregnancy and in postpartum state [11–14], in which it is called HELLP syndrome if an additional evidence of hepatitis is present [15–17], and with administration of drugs, such as quinine, cyclosporin A, mitomycin C, and oral contraceptives [10,11,18–22].

In our institution, eight cases of acute TTP have occurred following cardiac and vascular surgeries. In the literature, cases of acute TTP have been described following surgery, including liver and renal transplants, and resection of aneurysm [11,22–25], but there has been no well-documented case of TTP caused by cardiovascular surgery. Since recognition of this diagnosis is so crucial in the early postoperative period to attain uneventful recovery, the clinical features of cases with postoperative

Received for publication October 13, 1995; accepted March 6, 1996.

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TABLE I. Patient Clinical Data*

Patient no.	Age (year)/ race/sex	Surgery	Diagnosis of TTP (days postsurgery)	Treatment modality	Response	Final outcome
1	43/B/M	Femoral-popliteal artery bypass graft	5	PE (26)	Yes	CR
2	68/B/M	Vascular repair of injured neck vessels	17	PE (4)	No	Died
3	66/W/F	4 Vessel CABG	8	PE (2)	No	Died
4	59/W/M	3 Vessel CABG	7	PE (7)	Yes	CR
5	65/W/F	3 Vessel CABG and mitral valve repair	19	PE (2)	No	Died
6	76/W/M	3 Vessel CABG	12	PE (5)	Yes	CR
7	24/W/M	Resection of myocardial sarcoma	10	None	—	SR
8	68/W/F	3 Vessel CABG and valve replacement, mitral and tricuspid valve annuloplasty	8	PE (4)	Yes	CR

*CABG: coronary artery bypass graft; PE (no.): plasma exchange (number of PE in days); CR: complete remission; SR: spontaneous remission.

TTP are reviewed and possible pathogenic mechanism is discussed.

PATIENTS AND METHODS

A total of 47 patients with TTP were reviewed from Wright State University Affiliated Hospitals, Good Samaritan Hospital and Kettering Medical Center, from the duration between 1981 and 1995. The diagnostic criteria were based on the presence of MAHA and unexplained thrombocytopenia with or without neurologic abnormalities, fever, and renal failure. The possibility of consumption coagulopathy was excluded on the basis of normal fibrinogen level, prothrombin time and activated partial thromboplastin time, or other studies, including determination of levels of factors V and VIII, and fibrin degradation products. Also, heparin-induced thrombocytopenia was excluded according to previously described criteria, including the negative result of heparin-induced platelet aggregation test and lack of clinical relationship between heparin administration and thrombocytopenia [26]. The patients were subclassified to primary for idiopathic etiology and secondary for existence of an associated pertinent pathologic condition.

Among secondary cases of TTP, a total of 8 cases of postoperative TTP were identified. Their medical records were reviewed for clinical characteristics, including age, race, sex, surgical procedures, date of diagnosis after surgery, treatment modalities for TTP, response to the treatment, and final outcome. Hematologic data were also reviewed. These included hemoglobin, hematocrit, platelet count, reticulocyte count, and the level of haptoglobin and lactic dehydrogenase prior to surgery and after surgery. In addition, blood smears were reviewed, when available, for evaluation of the degree of schistocytosis. Its grading was estimated as follows: O for less than 1% of schistocytes among red blood cells, 1+ for 1–2%, 2+ for 2–5%, 3+ for 5–10%, and 4+ for more than 10%.

Also, evidence of neurological abnormalities was reviewed through examination of medical records, and existence of fever, development of renal function abnormalities, and evidence of thromboembolic complication determined.

RESULTS

Clinical Characteristics

Table I summarizes clinical characteristics of the patients with postoperative TTP. The age ranged between 24 and 76 years old. Six patients were white and two black. There were 5 men and 3 women. None of these patients had any significant underlying pathology that had previously been implicated for association with secondary TTP. Three patients underwent multivessel coronary artery bypass grafts (CABG), two CABG with valvular replacement or surgery, two vascular surgery, and one resection of myocardial sarcoma. Five patients who underwent CABG had severe coronary artery disease, and one patient had severe peripheral vascular disease. Two patients had no underlying cardiovascular disease, but one required extensive vascular repair surgery for stab wounds and another open heart surgery for resection of myocardial sarcoma.

The duration from the surgery to the diagnosis of TTP ranged between 5 to 19 days. All patients, except one patient (no. 7) who achieved spontaneous remission and the diagnosis was retrospectively established, were treated with exchange plasmapheresis. The treatment was

initiated as soon as the diagnosis of TTP was established. The number of days of exchange plasmapheresis ranged from 2 days to 26 days. When the patient was delayed in establishing the diagnosis, progressive neurological deterioration was the main influencing factor resulting in unfavorable outcome, and exchange plasmapheresis had no beneficial effects once the patient became comatose. Three patients who were in coma when exchange plasmapheresis was started died. Four patients responding to exchange plasmapheresis achieved complete and long-lasting remission.

Hematologic Features

As seen in Table II, prior to surgery 7 patients had normal hemoglobin, hematocrit, and platelet count and lack of schistocytes in the blood smear (Fig. 1A). Reticulocyte count and haptoglobin were either not performed or normal. However, 1 patient who had the stab wounds with laceration of multiple blood vessels had early signs of TTP, presumably due to vascular injury, with mild anemia, thrombocytopenia, 1+ schistocytosis, and low haptoglobin. Total white blood cell and differential white blood cell counts were normal in all patients. Following surgery, all patients developed evidence of MAHA and thrombocytopenia as shown in the blood slide (Fig. 1B). Microangiopathic hemolysis was confirmed by reticulocytosis, schistocytosis, and hypohaptoglobinemia. In addition, there were other laboratory features such as hyperbilirubinemia and increased level of lactic dehydrogenase to support the diagnosis of hemolysis. However, unlike classical TTP, the notable finding was rather a mild degree of schistocytosis, which ranged between 1+ and 2+.

Neurological, Renal, Febrile, and Other Clinical Features

All patients had neurological abnormalities. The major symptoms were gradual deterioration of mental functions, usually starting with confusion and disorientation and progressing to lethargy, drowsiness, somnolence, and eventual coma. One patient had seizures, motor aphasia, and hemiparesis. Initially, postoperative complications, such as cerebral infarction, intracranial hemorrhage, sepsis, cerebral abscess or infection, and side effects of drugs causing depression of the central nervous system, were often working diagnoses, and in all patients the diagnosis of TTP was established only after examination by the hematologist in hematologic consultation for unexplained thrombocytopenia. Non-responders to exchange plasmapheresis, which was likely due to delayed diagnosis and advanced disease, showed no improvement of comatose state and died. Responders showed rapid recovery of neurological functions as well as hematologic parameters.

All patients had normal blood urea nitrogen and serum creatinine prior to surgery. After surgery all patients showed modest elevation of blood urea nitrogen and se-

TABLE II. Patient Hematologic Data*

	Prior to surgery						Post surgery					
Patient no.	Hemoglobin (g %)	Hematocrit (%)	Platelets (μl)	Reticulocyte (%)	Blood smear (schistocytes)	Haptoglobin (mg %)	Hemoglobin (g %)	Hematocrit (%)	Platelets (μl)	Reticulocyte (%)	Blood smear (schistocytes)	Haptoglobin (mg %)
1	14.9	44.3	196,000	—	0	—	8.0	24.3	7,000	19.0	2+	10
2	11.8	33.6	64,000	—	1+	7	11.3	32.4	47,000	5.4	2+	<5
3	13.7	40.1	172,000	2.5	0	—	7.2	20.2	38,000	3.4	2+	12
4	15.2	45.5	231,000	—	0	65	7.4	21.2	66,000	8.3	1+	<5
5	13.1	40.9	421,000	—	—	74	8.7	24.5	23,000	7.6	2+	<5
6	16.0	45.0	185,000	—	0	—	9.3	27.4	39,000	12.5	2+	74
7	14.8	45.3	411,000	—	0	—	9.6	28.7	46,000	4.1	1+	38
8	14.1	42.8	276,000	—	0	—	8.4	24.2	55,000	9.1	1+	<5

*Control values: hemoglobin = 14–18 (male), 12–16 (female); hematocrit = 40–50 (male), 38–45 (female); platelets = 140,000–440,000; reticulocyte = 0.5–1.5; haptoglobin = 20–150. Schistocytes: 0 = less than 1%; 1+ = 1–2%; 2+ = 2–5%; 3+ = 5–10%; 4+ = more than 10%.

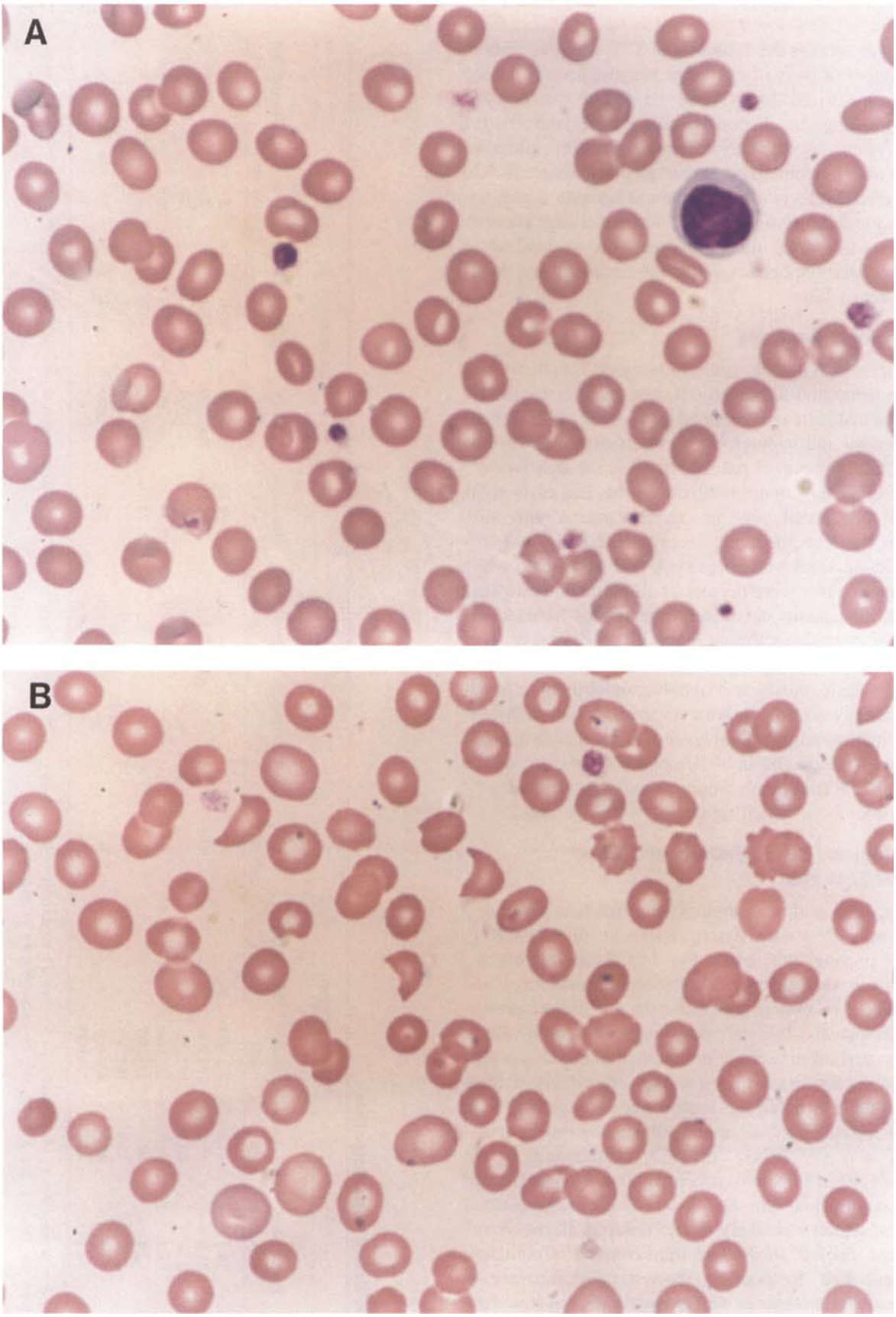

Fig. 1. The blood smear (×1,500) of patient no. 6 prior to multivessel coronary artery bypass graft (A). Please note that the red cell morphology is normal and no schistocyte is present. However, after surgery the blood smear shows some schistocytes with decreased platelets and prominent polychromasia (B).

rum creatinine, particularly during late stage of TTP in non-responders to exchange plasmapheresis. However, it is not certain whether or not these abnormalities were the result of progressive phase of postoperative TTP or a late complication of multiorgan failure. Low grade fever was present in most patients during active stage of TTP, but in view of complicated clinical features during postoperative stage, its significance couldn't be solely attributed to TTP.

Three patients (nos. 2, 3, and 8) developed progressive gangrene involving toes of both lower extremities, which worsened until their death in 2 patients and caused an amputation of a foot in 1 patient.

Illustrated Cases

Of 2 patients who underwent vascular surgery, the first patient (no. 1) was previously reported in the literature as a case report [27] of a 43-year-old man who was admitted for left femoro-popliteal bypass surgery for arteriosclerotic peripheral vascular disease. Five days after surgery the patient was established the diagnosis of TTP. The following classical features of the diagnosis were present: MAHA, neurologic abnormalities of motor aphasia and right hemiparesis, and acute thrombocytopenia with the platelet count of 7,000/μL. After 26 exchange plasmapheresis, the patient achieved complete remission. One and a half years later the patient again underwent aorto-bifemoral bypass graft for occlusive peripheral vascular disease. Four days after the surgery, TTP relapsed. The patient required a total of 35 exchange plasmapheresis during 12 weeks, and complete remission was achieved again.

The second patient (no. 2), who was a 68-year-old black man, was brought to the Emergency Room because of extensive stab wounds in the left side of the neck resulting in laceration of the external carotid artery, other blood vessels, and their branches. Although he was an alcoholic, he had no pre-existing hematologic condition and neurological disease prior to the stab-wound injury. Following extensive repair surgery, the patient developed fulminating TTP with acute thrombocytopenia and progression to coma. The diagnosis of TTP was delayed and the patient died in spite of initiation of exchange plasmapheresis. Initial hematologic data and blood slides were retrospectively reviewed. The first blood count when he was brought to the Emergency Room was abnormal. The patient apparently had MAHA, thrombocytopenia of 64,000/μL with presence of 1+ schistocytes and hypohaptoglobinemia. Prothrombin time and activated partial thromboplastin time were normal. In addition, the patient also developed progressive gangrene of the toes of both lower extremities. It was postulated that the patient developed TTP following extensive vascular injury from the stab wounds and further progressed to fulminating TTP during extensive vascular repair surgery.

The third patient (no. 8) was a 68-year-old white woman who underwent 3 vessel CABG with mitral valve replacement and tricuspid annuloplasty. Prior to surgery her hemogram was normal and blood smear showed no schistocytes. Two days after the surgery, the patient developed thrombocytopenia of 55,000/μL and MAHA with hypohaptoglobinemia and indirect hyperbilirubinemia. Three days after the surgery, she became confused, drowsy, and later semicomatose. On the 7th postoperative day, early gangrene of the toes of both feet, especially on the right, became apparent. Next day the diagnosis of TTP was established and exchange plasmapheresis begun when the platelet count was 45,000/μL. Two days later, the platelet count increased to 161,000/μL and mental condition began to improve. After 4 days of exchange plasmapheresis, her mental condition markedly improved, and later she underwent an amputation of the right forefoot for gangrene. Eight weeks after the open heart surgery, she was able to be discharged with complete remission of postoperative TTP.

DISCUSSION

Postoperative TTP is a unique syndrome, which has not yet been recognized as a disease entity in the literature. Our observation of occurrence of TTP in several patients after surgery, especially following cardiac and vascular surgeries, strongly supports the cause-effect relationship. Although there are anecdotal reports of TTP occurring after surgery, such as liver and renal transplants, and resection of aneurysm [11,22–25], the relationship between the surgery and development of TTP has been suspected on the basis of the clinical circumstance. On the contrary, all of our patients have had similar clinical features. They had no pre-existing hematologic abnormality with lack of pertinent underlying pathology, and underwent surgical procedures resulting in extensive cardiovascular or vascular endothelial injury. Also, the onset of TTP, although the diagnosis was delayed, was estimated to be within 2 to 5 days after the surgery in all patients. These are evidence that the surgery was the initiating event for acute TTP in 7 patients. In 1 patient (no. 2), acute TTP probably developed after multiple vascular injury, which worsened after extensive vascular repair surgery.

In some of our patients, the diagnosis of TTP was delayed because this disease was not considered even though the patients had anemia, thrombocytopenia, and neurologic changes because these changes commonly occur as the result of blood loss from surgery, transfusion, drug administration, and other complication of surgery such as infection, hypoxia, hypovolemia, and metabolic abnormalities. In addition, unlike classical TTP, evidence of microangiopathy was subtle in these patients because schistocytes were present not in an overwhelming number

when the blood smears were examined. Nonetheless, there was appearance of schistocytes and thrombocytopenia that were not present preoperatively. Increased reticulocyte count and decreased haptoglobin along with other evidence of hemolysis confirmed the diagnosis of MAHA. Undoubtedly, inattention to these findings and lack of consideration of TTP contributed to the failure of early diagnosis and lost precious time, which resulted in death in some patients. According to our experience, exchange plasmapheresis is highly effective in early stage of postoperative TTP as was previously reported for classical TTP [1–5].

Pathogenesis of TTP is unknown. The clinical observation of secondary TTP in certain patients with collagen vascular disease, bacterial endocarditis, hypersensitivity drug reaction and postoperative state of cardiovascular surgery, and characteristic vascular changes of microthrombi without evidence of inflammation suggest that vascular endothelium, whether its pathology is related to the disease or physical injury, may play a crucial role.

The endothelial cells forming the luminal vascular surface are strategically positioned to take an important part in the regulation of coagulation. These cells provide both anticoagulant and procoagulant properties, including synthesis of thrombomodulin to serve in the anticoagulant pathway and maintenance of a low level of tissue factor to inhibit the unwarranted procoagulant pathway [28,29]. Also, the endothelial cell is the predominant site for production and storage of von Willebrand factor (vWF) [30,31]. In patients with advanced vascular endothelial disease or undergoing extensive cardiovascular surgery, diseased or injured endothelial cells may result in decreased thrombomodulin synthesis, enhanced induction of tissue factor, and production of abnormal multimeric forms of vWF. Decreased thrombomodulin level would cause inefficient protein C-dependent anticoagulant pathway, and increased tissue factor supply would cause activation of factor VII on the endothelial surface. Both situations, with participation of abnormal vWF multimers that serve as an adhesive ligand between platelets and injured or diseased vascular elements [32], would produce intravascular thrombosis, which may be the basis of pathogenesis for postoperative of TTP.

In the era of more aggressive cardiac and vascular surgery as the result of a benefit of advancing intervention technology, postoperative TTP may occur more frequently in this modern age of medicine. Postoperative TTP can be defined as an acute life-threatening hematologic complication of surgery that is characterized by MAHA with mild to modest schistocytosis, thrombocytopenia, and neurologic abnormalities. It should be emphasized that postoperative TTP has occurred after cardiac and vascular surgeries. Postoperative TTP syndrome should be one of the differential diagnoses for postsurgical patients who present with unexplained anemia, thrombocytopenia, and neurological symptoms and signs. It is important to note that development of gangrene in the lower extremities has occurred in some patients. Since early diagnosis and institution of exchange plasmapheresis is critically important for favorable outcome, hematologic evaluation, including examination of blood slides, a serial platelet count, reticulocyte count, determination of haptoglobin level, and other studies such as lactic dehydrogenase and bilirubin level, should be performed at the earliest possible time.

ACKNOWLEDGMENTS

The authors thank Patricia Myers for special editorial assistance in the preparation of this manuscript. This work has been supported in part by a grant from Samaritan Health Foundation.

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